Magellan Rx MANAGEMENT

Clinical Alert

June 2017

New Hepatitis C Virus (HCV) Statistics in the United States (U.S.)

The Centers for Disease Control and Prevention (CDC) has reported that the incidence of new HCV infection in the U.S. has nearly tripled in just 5 years, bringing the prevalence to its highest level in 15 years. This statistic is based on preliminary surveillance data collected between 2010 and 2015 and includes 2,436 new cases reported to the CDC in 2015; however, the CDC believes that new cases are under reported due to limited surveillance resources and the fact that HCV infection is asymptomatic in as many as 50% of people with the condition, causing it to go undiagnosed. The CDC estimates that the number of new cases in 2015 was closer to 34,000.

The largest increase in new HCV cases was detected in younger (ages 20 to 29 years) Caucasians in non-urban areas. The majority of the increase is attributed to a rise in injectable drug use in the U.S. and, to a lesser extent, improved detection. The CDC also reports that, between 2009 and 2014, HCV infection rose among women of childbearing age. In states that reported HCV on birth certificates, this number increased 89% from 1.8 to 3.4 per 1,000 live births. Notably, West Virginia and rural areas of Tennessee that are greatly impacted by heroin and opioid addiction had the sharpest increases.

There are a total of 3.5 million Americans living with HCV. Although the spread of HCV is rapidly growing in the younger population, the majority of cases of HCV are among baby boomers, those born between 1945 and 1965, who are at greater risk of death from the disease. The CDC reports that, in 2015 alone, there were nearly 20,000 HCV-related deaths in the U.S.

The CDC states that comprehensive methods are needed to combat the opioid epidemic and injection-related infectious diseases. Strategies include syringe service programs and improved access to drug abuse treatment, rehabilitation services, infectious disease testing, and medical care.

AUA/ASTRO/SUO Releases Prostate Cancer Guidelines

The American Urological Association (AUA), American Society for Radiation Oncology (ASTRO), and Society of Urologic Oncology (SUO) released updated prostate cancer guidelines. The guidelines emphasize shared decision making and stratify recommendations by cancer severity and risk group. Patients should be counseled on the immediate- and long-term morbidity and adverse effects of treatment options. For patients with very low- or low-risk localized disease, the guidelines recommend active surveillance, while radical prostatectomy or radiotherapy plus androgen deprivation therapy (ADT) are recommended for patients with intermediate- or high-risk disease. However, watchful waiting is recommended in those with intermediate-risk and a life expectancy of 5 years or less and can also be considered in those with high-risk disease and a limited life expectancy. Definitive treatment (e.g., radical prostatectomy or radiotherapy) may also be considered in select low-risk, localized prostate cancer patients with a high probability of progression on active surveillance. Following treatment, disease recurrence should be monitored with prostate-specific antigen (PSA) testing, although not all PSA recurrences are associated with metastatic disease.

The complete guidelines are available at http://www.auanet.org.

Drug Information Highlights

- The Food and Drug Administration (FDA) approved a second biosimilar to Janssen's infliximab (Remicade®); infliximab-abda (Renflexis™) by Samsung Bioepsis. It is approved for all indications as Remicade, except pediatric ulcerative colitis.
- The programmed death ligand-1 (PD-L1) inhibitor, avelumab (Bavencio®), was granted FDA-approval for locally advanced or metastatic urothelial carcinoma in patients who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Avelumab is already approved for patients with Merkel cell carcinoma (MCC). The dosage for both indications is 10 mg/kg by intravenous (IV) infusion every 2 weeks.
- Nivolumab (Opdivo®), a programmed death receptor-1 (PD-1) inhibitor, received an accelerated approval for the treatment of classical Hodgkin lymphoma (CHL) in adults who have relapsed or progressed after ≥ 3 lines of systemic therapy that included autologous hematopoietic stem cell transplantation (HSCT). Previously, it was only indicated in patients in this population who had relapsed or progressed after autologous HSCT and brentuximab vedotin. Nivolumab is also approved for select patients with melanoma, non-small cell lung cancer (NSCLC), advanced renal cell carcinoma (RCC), squamous cell carcinoma, and urothelial carcinoma. The dosage for CHL is 3 mg/kg every 2 weeks by IV infusion.
- An alternative starting dose regimen was approved for alirocumab (Praluent®) of 300 mg subcutaneously (SC) once monthly, administered as two 150 mg injections at 2 different sites. The approval of this new regimen is based on data from the ODYSSEY CHOICE I study. It was previously approved as a 75 mg SC injection administered every 2 weeks. Either regimen may be adjusted to 150 mg every 2 weeks if the clinical response is inadequate.
- The FDA expanded the approval of buprenorphine/naloxone buccal film (Bunavail®) to include the initiation of buprenorphine treatment for opioid dependence, in addition to maintenance treatment. To avoid precipitating withdrawal, induction therapy should begin when objective signs of withdrawal are clear.
- The Risk Evaluation and Mitigation Strategy (REMS) program that has been required for use in cancer patients was eliminated for erythropoiesis stimulating agents (darbepoetin [Aranesp®] and epoetin [Epogen®, Procrit®]).

Practice Parameter Updated for Sublingual Immunotherapy (SLIT)

The American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) have released a practice parameter update on the appropriate use of SLIT. The joint recommendations are based on direct evidence and/or accepted consensus opinion.

At the time these guidelines were developed, there were 3 products approved by the FDA for SLIT in the U.S., including Grastek® and Oralair® for the treatment of grass pollen-induced allergic rhinitis and Ragwitek® for the treatment of ragweed pollen-induced allergic rhinitis. Subsequently, Odactra® has been FDA-approved for the management of house dust mite allergy, but it is not specifically discussed in the practice parameters. Notably, all agents are indicated for use only after a confirmatory skin test or IgE antibody test. All 4 products are taken as 1 sublingual tablet once daily. Grastek and Ragwitek are started at least 12 weeks prior to the anticipated start of the pollen season; Oralair is started 4 months before pollen season onset. Grastek, Ragwitek, and Oralair are continued throughout their respective pollen seasons; while Odactra is administered year round.

The AAAAI/ACAAI state that the FDA-approved products should only be used for the treatment of their labeled indications; they should not be used for allergies to food, latex, or venom, or for atopic dermatitis. Similar to the product labeling, AAAAI/ACAAI advises that SLIT is not appropriate for any patient with a medical condition that may reduce their ability to survive a systemic reaction or the treatment of the systemic reaction. These reactions include, but are not limited to, markedly compromised lung function; severe, unstable, or uncontrolled asthma; eosinophilic esophagitis; unstable angina or recent myocardial infarction; significant arrhythmia; uncontrolled hypertension; and prior systemic reaction to immunotherapy. SLIT must be initiated in a medical facility under the supervision of a healthcare provider (HCP) experienced in diagnosing and treating anaphylaxis, but subsequent doses may be self-administered. Likewise, an epinephrine auto-injector should also be prescribed to all patients on SLIT. The dosing equivalence of SLIT tablets and aqueous allergen extracts should not be assumed; each product must establish its own safety profile. While data on the 3 pollen-related products vary, the group recommends a dose reduction in patients who miss more than 7 consecutive daily doses. Finally, similar to injectable immunotherapy (SCIT), response to SLIT should be assessed on a regular basis to monitor for safety, efficacy, and adherence.

Detailed guidelines are available at https://www.aaaai.org.

Joint Guideline Provides Management Recommendations for Syncope

The American College of Cardiology (ACC), American Heart Association (AHA), and the Heart Rhythm Society (HRS) published a joint guideline that systematically reviewed evidence to define, evaluate, diagnose, and treat adult and pediatric patients with suspected syncope. The guideline, which was also developed in collaboration with the American College of Emergency Physicians (ACEP) and Society for Academic Emergency Medicine (SAEM) and endorsed by the Pediatric and Congenital Electrophysiology Society (PACES), defines syncope as a symptom that presents with an abrupt, transient, and complete loss of consciousness associated with inability to maintain postural tone, with rapid and spontaneous recovery. They further define various subtypes of syncope within the full publication.

ACC/AHA/HRS recommend guideline-directed management and therapy (GDMT) comprising clinical evaluation, diagnostic testing, and pharmacological and procedural treatments. Pharmacotherapy guidance for syncope management is based on syncope etiology. Key recommendations include the use of beta-blockers for patients with long QT syndrome and suspected arrhythmic syncope, unless contraindicated. Beta-blockers that lack intrinsic sympathomimetic activity are recommended for patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) and stress-induced syncope. Verapamil, with or without beta-blockers, and flecainide are also reasonable choices for patients with CPVT and continued syncope. For recurrent vasovagal syncope (VVS), reasonable options include beta-blockers, midodrine, fludrocortisone, droxidopa, and selective serotonin reuptake inhibitors (SSRI), depending on patient characteristics such as age, history of hypertension, heart failure, urinary retention, neurogenic orthostatic hypotension, and response to salt/fluid intake. In addition, pyridostigmine and octreotide may be helpful in treatment-refractory patients.

Treatment of syncope is also dependent on nonpharmacotherapy. Complete guidelines are available at http://www.onlinejacc.org.

- The FDA issued a Drug Safety Communication regarding codeine and tramadol to restrict use in children and recommend against use in breastfeeding women. All labels of codeine- and tramadol-containing products will include a contraindication against their use in children < 12 years of age due to an increased risk of slowed or difficult breathing, and a warning against their use in adolescents (ages 12 to 18 years) who may be at an increased risk of respiratory concerns. A contraindication will also be added to tramadol-containing products stating they should not be used in children < 18 years old for adenoid and/or tonsil post-surgical pain. In addition, the warning was strengthened regarding the use of either drug in breastfeeding women due to the potential for excess sleepiness, difficulty feeding, or death in the infant.
- A new indication was awarded to regorafenib (Stivarga®) for the treatment of hepatic cellular carcinoma (HCC) in patients who have previously been treated with sorafenib. Regorafenib is also approved for metastatic colorectal cancer and gastrointestinal stromal tumors (GIST) in select populations.

Pipeline News: Upcoming Prescription Drug User Fee Act (PDUFA) Dates

- **June, 2017:** Berinert; CSL830; SC low-volume C1-esterase inhibitor; hereditary angioedema; CSL Behring.
- **June, 2017:** Mekinist®; trametinib; oral kinase inhibitor; BRAF V600+ NSCLC; Novartis.
- **June, 2017:** Tafinlar®; dabrafenib; oral kinase inhibitor; BRAF V600+ NSCLC; Novartis.
- **June 5, 2017:** Aristada®; aripiprazole lauroxil (2 month dosing regimen); oral atypical antipsychotic; schizophrenia; Alkermes.
- **June 17, 2017:** Darzalex®; daratumumab; IV anti-CD38 antibody; multiple myeloma in combination with pomalidomide and dexamethasone; Janssen/Genmab.
- **June 19, 2017:** Baxdela; delafloxacin; oral/IV fluoroquinolone antibiotic; acute bacterial skin and skin structure infections; Abbvie/Melinta/Ligand.
- **June 20, 2017:** dextroamphetamine/amphetamine; oral central nervous system stimulant; attention deficit hyperactivity disorder (ADHD); Shire.
- **June 24, 2017:** betrixaban; direct-acting oral anticoagulant; venous thromboembolism; Portola.
- **June 26, 2017:** Rituxan SC; rituximab/hyaluronidase; SC anti-CD20 antibody; follicular lymphoma, diffuse large B cell lymphoma, chronic lymphocytic leukemia; Genentech/Roche.
- **June 30, 2017:** binimetinib; oral MEK inhibitor; melanoma; Array Biopharma.
- **Quarter 2, 2017:** ozenoxacin; topical non-fluorinated quinolone antibiotic; impetigo; Ferrer/Medimetriks.

Recent FDA Approvals

Generic Name	Trade Name	Description	Applicant	FDA Status
oxycodone immediate-release	Roxybond™	The FDA has approved the first abuse-deterrent immediate-release formulation of oxycodone, Roxybond, for the management of pain severe enough to require an opioid analgesic for which alternative treatments are inadequate or not tolerated. It is formulated with SentryBond™ technology that uses physical and chemical barriers to prevent abuse. Initial dose is 5 mg to 15 mg every 4 to 6 hours as needed for pain. The Schedule CII product is approved as 5 mg, 15 mg, and 30 mg tablets.	Inspirion	FDA NDA approval 04/20/2017
methotrexate	Xatmep™	The first oral solution formulation of methotrexate (Xatmep) was approved for the treatment of pediatric patients with acute lymphoblastic leukemia (ALL) in conjunction with a combination chemotherapy maintenance regimen. It was also approved for the management of active polyarticular juvenile idiopathic arthritis (pJIA) in patients who are intolerant or who have had an inadequate response to first-line agents. The recommended starting dose for ALL is 20 mg/m^2 orally once weekly. For the treatment of pJIA, the starting dose is 10 mg/m^2 once weekly. The risk of toxic reactions increases with doses > 20 mg/m^2/week. Xatmep was given Orphan Drug designation and is approved as a 2.5 mg/mL oral solution.	Silvergate	FDA NDA approval 04/25/2017
cerliponase alfa	Brineura™	The FDA approved cerliponase alfa (Brineura), a lysosomal N-terminal tripeptidyl peptidase. It is the first treatment to slow the loss of ambulation in symptomatic pediatric patients ≥ 3 years of age with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase-1 (TPP1) deficiency, a form of Batten disease. The recommended dose of 300 mg (10 mL) is administered using aseptic technique by an HCP into the cerebrospinal fluid (intraventricular [IVT] infusion); this is followed by IVT infusion of the electrolyte solution (2 mL of a 5 mL vial) provided in the co-package. Total infusion time is approximately 4.5 hours. Cerliponase alfa was granted Breakthrough Therapy and Orphan Drug designations.	Biomarin	FDA BLA priority approval 04/27/2017
abaloparatide	Tymlos™	Abaloparatide (Tymlos) was approved for the treatment of osteoporosis in postmenopausal women who are at high risk for fractures. It carries a boxed warning due to the potential risk of osteosarcoma. This synthetic analog of human parathyroid hormone-related peptide (PTHr [1-34]) is self-administered in the periumbilical region of the abdomen as 80 mcg (40 mcL) SC once daily. The prefilled pen contains 3,120 mcg/1.56 mL and delivers 30 daily doses. Lifetime cumulative use of parathyroid hormone analogs (e.g., abaloparatide and teriparatide) beyond 2 years is not recommended.	Radius Health	FDA NDA approval 04/28/2017
brigatinib	Alunbrig™	The FDA granted accelerated approval, based on tumor response rate and duration of response, to the kinase inhibitor brigatinib (Alunbrig) for the treatment of anaplastic lymphoma kinase (ALK)-positive metastatic NSCLC in patients who have progressed on or are intolerant to crizotinib. Continued approval may be contingent upon results of a confirmatory trial. Brigatinib is administered, with or without food, as 90 mg once daily for 7 days; the dose can then be increased to 180 mg daily as tolerated. It is administered until the disease progresses or toxicity is unacceptable. It is approved as 30 mg and 90 mg tablets. Brigatinib was given Breakthrough Therapy and Orphan Drug designations.	Ariad	FDA NDA priority approval 04/28/2017
midostaurin	Rydapt®	Midostaurin (Rydapt) was approved, in combination with chemotherapy, as the first targeted therapy for newly diagnosed, FMS-like tyrosine kinase 3 mutation-positive (FLT3+) acute myeloid leukemia (AML). It was also approved for the treatment of advanced systemic mastocytosis (SM), including aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL). Breakthrough Therapy was granted for AML and Orphan Drug for both indications. Approved as a 25 mg oral capsule, the recommended dose is 50 mg twice daily for AML and 100 mg twice daily for ASM, SM-AHN, and MCL; it should be taken with food.	Novartis	FDA NDA priority approval 04/28/2017
durvalumab	Imfinzi™	The PD-L1 inhibitor durvalumab (Imfinzi) received Breakthrough Therapy designation and accelerated approval for locally advanced or metastatic urothelial cancer in patients with disease progression during or following platinum-containing chemotherapy, or within 12 months of receiving neoadjuvant or adjuvant platinum-containing chemotherapy. The recommended dose is 10 mg/kg as an IV infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity occurs. It is approved as 500 mg/10 mL and 120 mg/2.4 mL single-dose vials.	AstraZeneca	FDA BLA approval 05/01/2017

ANDA = Abbreviated New Drug Application; BLA = Biologics License Application; NDA = New Drug Application; sBLA = Supplemental Biologics License Application; sNDA = Supplemental New Drug Application

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References

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